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1: Rev Med Chil. 1991 Dec;119(12):1423-32.

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[Pharmacologic treatment of dyslipidemias: Analysis of initiation recommendations and drug selection]

[Article in Spanish]

Davidoff P.

Departamento de Medicina, Facultad de Medicina, Universidad de Chile (Division Occidente), Hospital San Juan de Dios, Santiago de Chile.

According to the NCEP resins and nicotinic acid were selected as drugs of choice to treat hypercholesterolemia. Gemfibrozil and nicotinic acid were recommended for patients with HDL cholesterol below 35 mg/dl. Current concepts of efficacy and side effects lead to the following recommendations. a) type IIa severe hypercholesterolemia (LDL > 220 mg/dl): HGMC inhibitors or combined therapy with resins and nicotinic acid, fenofibrate, or bezafibrate. b) Moderate hypercholesterolemia (LDL < 220 mg/dl): bezafibrate and/or acipimox if HDL is < 35 mg/dl; fenofibrate, bezafibrate and/or acipimox if HDL > 35 mg/dl. As second line drugs, the HGMC inhibitors. c) Type IIb hyperlipidemia: first line, acipimox; second line, fibrates associated to acipimox. d) Type III hyperlipidemia: first line, fibrates second line, an association of HGMC inhibitors and fibrates or acipimox. e) Type IV moderate hyperlipidemia (TG < 500 mg/dl): first line, acipimox, second line, fibrates alone or in association with acipimox. As general remarks, lovastatin has been effective and well tolerated in 98% of cases. Pravastatin seems to have very little side effects. Acipimox, a nicotinic acid derivative is especially effective in elevating HDL2b levels and decreasing LDL III. Given its adequate tolerance, acipimox has replaced nicotinic acid.

Publication Types:
- Review
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Stedman's Dictionary

Define: Search

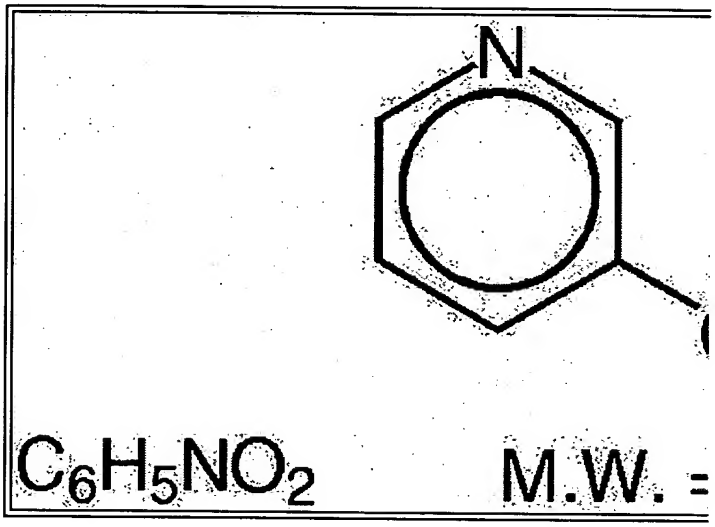
Document Outline

PDR® entry for

NIASPAN® (Kos)
niacin extended-release tablets
Rx Only

DESCRIPTION

NIASPAN® (niacin extended-release tablets), contain niacin, a B antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarl crystalline powder, very soluble in water, with the following stru



NIASPAN® is an unscored, off-white tablet for oral administratio additives and is available in three tablet strengths containing 50 NIASPAN tablets also contain the inactive ingredients methylcell acid.

(*back to top*)

CLINICAL PHARMACOLOGY

Niacin functions in the body after conversion to nicotinamide ade NAD coenzyme system. Niacin (but not nicotinamide) in gram dc (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride density lipoprotein cholesterol (HDL-C). The magnitude of the in responses may be influenced by the severity and type of underly

increase in total HDL-C is associated with an increase in apolipo
in the distribution of HDL subfractions. These shifts include an in
ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle
Niacin treatment also decreases serum levels of apolipoprotein E
protein component of the very low-density lipoprotein (VLDL) an
variant form of LDL independently associated with coronary risk.
reports suggest that niacin causes favorable LDL particle size tra
clinical relevance of this effect requires further investigation. The
changes in lipids/lipoproteins on cardiovascular morbidity or mo
pre-existing coronary disease has not been established.

A variety of clinical studies have demonstrated that elevated lev
promote human atherosclerosis. Similarly, decreased levels of H
development of atherosclerosis. Epidemiological investigations h
cardiovascular morbidity and mortality vary directly with the lev
inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, inclu
density lipoprotein (IDL), and remnants, can also promote ather
are frequently found in a triad with low HDL-C levels and small L
association with non-lipid metabolic risk factors for coronary hea
plasma TG has not consistently been shown to be an independer
Furthermore, the independent effect of raising HDL-C or lowerin
and cardiovascular morbidity and mortality has not been determ

Mechanism of Action

The mechanism by which niacin alters lipid profiles has not been
several actions including partial inhibition of release of free fatty
increased lipoprotein lipase activity, which may increase the rate
removal from plasma. Niacin decreases the rate of hepatic synth
does not appear to affect fecal excretion of fats, sterols, or bile a

Pharmacokinetics/Metabolism

Absorption

Niacin is rapidly and extensively absorbed (at least 60 to 76% o
orally. To maximize bioavailability and reduce the risk of gastroi
administration of NIASPAN with a low-fat meal or snack is recom

Single-dose bioavailability studies have demonstrated that NIAS
interchangeable.

Distribution

Studies using radiolabeled niacin in mice show that niacin and it
the liver, kidney and adipose tissue.

Metabolism

The pharmacokinetic profile of niacin is complicated due to rapid

metabolism, which is species and dose-rate specific. In humans, simple conjugation step with glycine to form nicotinuric acid (NU urine, although there may be a small amount of reversible meta other pathway results in the formation of nicotinamide adenine c whether nicotinamide is formed as a precursor to, or following th Nicotinamide is further metabolized to at least N-methylnicotinai N-oxide (NNO). MNA is further metabolized to two other compou carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4F appears to predominate over 4PY in humans. At the doses used metabolic pathways are saturable, which explains the nonlinear dose and plasma concentrations following multiple-dose NIASPA

Nicotinamide does not have hypolipidemic activity; the activity o unknown.

Table 1. Mean Steady-State Pharmacokinet Plasma Niacin

NIASPAN		Nia
dose/day	given as	Peak Concentration (µg/mL)
1000mg	2 × 500mg	0.6
1500mg	2 × 750mg	4.9
2000mg	2 × 1000mg	15.5

Elimination

Niacin and its metabolites are rapidly eliminated in the urine. Fo doses, approximately 60 to 76% of the niacin dose administered urine as niacin and metabolites; up to 12% was recovered as un dosing. The ratio of metabolites recovered in the urine was depe administered.

Special Populations

Hepatic

No studies have been performed. NIASPAN should be used with history of liver disease, who consume substantial quantities of al transaminase elevations. NIASPAN is contraindicated in patients WARNINGS).

Renal

There are no data in this population. NIASPAN should be used w renal disease (see PRECAUTIONS).

Gender

Steady-state plasma concentrations of niacin and metabolites af
are generally higher in women than in men, with the magnitude
dose and metabolite. Recovery of niacin and metabolites in urine
for men and women, indicating that absorption is similar for botl
differences observed in plasma levels of niacin and its metabolit
specific differences in metabolic rate or volume of distribution. D
suggest that women have a greater hypolipidemic response thar
NIASPAN.

Niacin Clinical Studies

The role of LDL-C in atherogenesis is supported by pathological
and many animal experiments. Observational epidemiological st
that high TC or LDL-C and low HDL-C are risk factors for CHD. A
Lp(a) have been shown to be independently associated with CHI
improving lipoprotein lipid profiles, either alone or in combinatio
drugs, as an adjunct to diet therapy in the treatment of hyperlip
documented.

Niacin's ability to reduce mortality and the risk of definite, nonfa
has also been assessed in long-term studies. The Coronary Drug
was designed to assess the safety and efficacy of niacin and oth
30 to 64 years old with a history of MI. Over an observation peri
was associated with a statistically significant reduction in nonfat
of definite, nonfatal MI was 8.9% for the 1,119 patients random
12.2% for the 2,789 patients who received placebo (p <0.004).
the two groups at 5 years (24.4% with nicotinic acid versus 25.
the time of a 15-year follow-up, there were 11% (69) fewer dea
compared to the placebo cohort (52.0% versus 58.2%; p =0.00
years was not an original endpoint of the Coronary Drug Project.
received niacin for approximately 9 years, and confounding varia
medication use and medical or surgical treatments were not con

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a ra
angiographic trial testing combined colestipol and niacin therapy
with previous coronary bypass surgery. [4] The primary, per-subje
coronary artery change score. After 2 years, 61% of patients in
disease progression by global change score (n=82), compared w
subjects (n=80), when both native arteries and grafts were cons
regression also occurred more frequently in the drug-treated grc
=0.002). In a follow-up to this trial in a subgroup of 103 patient
significantly fewer patients in the drug-treated group demonstra
placebo cohort (48% versus 85%, respectively; p <0.0001). [5]

The Familial Atherosclerosis Treatment Study (FATS) in 146 mer
Apo B levels >/=125 mg/dL, established coronary artery disease
vascular disease, assessed change in severity of disease in the p
quantitative arteriography. [6] Patients were given dietary counsel
treatment with either conventional therapy with double placebo
the LDL-C was elevated); lovastatin plus colestipol; or niacin plu
conventional therapy group, 46% of patients had disease progre
least one of nine proximal coronary segments; regression was th
contrast, progression (as the only change) was seen in only 25%

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group, while regression was observed in 39%. Though not an or clinical events (death, MI, or revascularization for worsening anc patients who received conventional therapy, compared with 2 of colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP) was a r 2.5-year study of the effect of a stepped-care antihyperlipidemic (80 men and 11 women) with CHD and average baseline TC leve ratios of TC to HDL-C greater than 4.0. [7] Drug treatment consist inhibitor administered alone as initial therapy followed by additic a slow-release nicotinic acid, cholestyramine, or gemfibrozil. Adc HMG-CoA reductase inhibitor resulted in further statistically sign LDL-C, and TG, as well as a further increase in HDL-C in a major patients). The ratios of TC to HDL-C and LDL-C to HDL-C were a combination drug regimen (see WARNINGS , *Skeletal Muscle*).

NIASPAN Clinical Studies

Placebo-controlled Clinical Studies in Patients with Primary Hype Dyslipidemia: In two randomized, double-blind, parallel, multi- trials, NIASPAN dosed at 1000, 1500 or 2000mg daily at bedtim weeks (including 4 weeks of dose escalation) favorably altered li placebo (Table 2). Women appeared to have a greater response dose level (see *Gender Effect* , below).

Table 2. Lipid Response to NIASPAN

		Mean Percent Change from B				
Treatment	n	TC	LDL-C	HDL-C	TC/HDL-C	
NIASPAN 1000mg qhs	41	-3	-5	+18	-17	
NIASPAN 2000mg qhs	41	-10	-14	+22	-25	
Placebo	40	0	-1	+4	-3	
NIASPAN 1500mg qhs	76	-8	-12	+20	-20	
Placebo	73	+2	+1	+2	+1	

n = number of patients at baseline;

* Mean percent change from baseline for all NIASP significantly different ($p < 0.05$) from placebo for a shown except Apo A-1 at 2000mg.

In a double-blind, multi-center, forced dose-escalation study, m NIASPAN dose resulted in incremental reductions of approximate levels in the daily dose range of 500mg through 2000mg (Table have a greater response to NIASPAN than men (see *Gender Effe*

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Table 3. Lipid Response in Dose-Escal

Treatment		Mean Percent Change f			
	n	TC	LDL-C	HDL-C	TC/HDL-C
Placebo ‡	44	-2	-1	+5	-7
NIASPAN	87				
500mg qhs		-2	-3	+10	-10
1000mg qhs		-5	-9	+15	-17
1500mg qhs		-11	-14	+22	-26
2000mg qhs		-12	-17	+26	-29

n = number of patients enrolled;

‡ Placebo data shown are after 24 weeks of placebo

* For all NIASPAN doses except 500mg, mean perc baseline was significantly different (p <0.05) from parameters shown except Lp(a) and Apo A-1 which different from placebo starting with 1500mg and 2(

Pooled results for major lipids from these three placebo-controlle (Table 4).

Table 4. Selected Lipid Response to NIASPAN in Pl Studies *

		Mean Baseline and Median Perce (25 th , 75 th Per	
NIASPAN Dose	n	LDL-C	HDL-C
1000mg qhs	104		
Baseline (mg/dL)		218	45
Percent Change		-7 (-15, 0)	+14 (+7,+
1500mg qhs	120		
Baseline (mg/dL)		212	46
Percent Change		-13 (-21,-4)	+19 (+9,+
2000mg qhs	85		

Baseline (mg/dL)		220	44
Percent Change		-16 (-26,-7)	+22 (+15,-

* Represents pooled analyses of results; minimum d each dose was 4 weeks.

Gender Effect: Combined data from the three placebo-controll with primary hypercholesterolemia and mixed dyslipidemia sugg level studied, changes in lipid concentrations are greater for wor

Table 5. Effect of Gender on NIASPAN D

		Mean Percent Chang				
		LDL-C		HDL-C		
NIASPAN Dose	n (M/F)	M	F	M	F	
500mg qhs	50/37	-2	-5	+11	+8	-
1000mg qhs	76/52	-6 *	-11 *	+14	+20	1
1500mg qhs	104/59	-12	-16	+19	+24	1
2000mg qhs	75/53	-15	-18	+23	+26	3

n = Number of male/female patients enroll

* Percent change significantly different betv (p <0.05).

Long-term Study: In a recently completed long-term open-lab hypercholesterolemia and mixed dyslipidemia received NIASPAN response and tolerance. An HMG-CoA reductase inhibitor or a bil added to NIASPAN therapy for patients whose response to NIASI qhs) was insufficient, or who would not tolerate higher niacin do 96 weeks of treatment (Table 6) suggest combination therapy e response (see WARNINGS , *Skeletal Muscle*).

niacin/c acid + HMG CoA red. inhibitor

Table 6. NIASPAN Efficacy with Combin

			Mean Percent Ch			
Treatment	Duration	n	TC	LDL-C	HDL-C	TC

	Baseline	185	-	-	-	
NIASPAN Alone	48 weeks	101	-11	-18	+29	
	96 weeks	74	-10	-18	+32	
	Baseline	53	-	-	-	
NIASPAN & HMG-CoA	48 weeks	45	-23	-32	+26	
	96 weeks	37	-24	-32	+25	
	Baseline	16	-	-	-	
NIASPAN & BAS	48 weeks	15	-11	-20	+36	
	96 weeks	7	-15	-28	+31	

Note: Median NIASPAN dose was 2000mg qhs in ea
duration of HMG-CoA combination therapy was app
Mean duration of BAS combination therapy was apr

* number of patients (n) are up to 33% lower at ba
weeks; na = data are not available.

Other Patient Populations: In a double-blind, multi-center, 19-
effects of NIASPAN (forced titration to 2000mg qhs) were compa
whose primary lipid abnormality was a low level of HDL-C (HDL-
mg/dL, and LDL-C</=160, or <130 mg/dL in the presence of CH
(Table 7).

Table 7. Lipid Response to NIASPAN in Patien

		Mean Baseline and Mean Percent					
	n	TC	LDL-C	HDL-C	TC/HDL-C	TG	(a
Baseline (mg/dL)	88	190	120	31	6	194	
Week 19 (% Change)	71	-3	0	+26	-22	-30	-

n = number of patients enrolled
* Mean percent change from baseline was significa
<0.05) for all lipid parameters shown except LDL-C

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† n=72 at baseline and 69 at week 19.

‡ n=30 at baseline and week 19.

At NIASPAN 2000 mg/day, median changes from baseline (25 th HDL-C, and TG were -3% (-14, +12%), +27% (+13, +38%), ar respectively.

(*back to top*)

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one componen intervention in individuals at significantly increased risk for athe to hypercholesterolemia. Niacin therapy is indicated as an adjun a diet restricted in saturated fat and cholesterol and other nonpl has been inadequate (see also the NCEP treatment guidelines [8]) with niacin, secondary causes for hypercholesterolemia (e.g., po mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, drug therapy, alcoholism) should be excluded, and a lipid profile C, and TG.

adj. therapy

1. NIASPAN is indicated as an adjunct to diet for reduction of TG levels, and to increase HDL-C in patients with primary I (heterozygous familial and nonfamilial) and mixed dyslipid and IIb; Table 8), when the response to an appropriate die
2. In patients with a history of myocardial infarction and hyp indicated to reduce the risk of recurrent nonfatal myocardi
3. In patients with a history of coronary artery disease (CAD) niacin, in combination with a bile acid binding resin, is indi promote regression of atherosclerotic disease.
4. NIASPAN in combination with a bile acid binding resin is in for reduction of elevated TC and LDL-C levels in adult patie hypercholesterolemia (Type IIa; Table 8), when the respor diet plus monotherapy, has been inadequate.
5. Niacin is also indicated as adjunctive therapy for treatmen high serum triglyceride levels (Types IV and V hyperlipider risk of pancreatitis and who do not respond adequately to control them. Such patients typically have serum TG levels elevations of VLDL-C as well as fasting chylomicrons (Type Patients who consistently have total serum or plasma TG t to develop pancreatitis. Therapy with niacin may be consid elevations between 1000 and 2000 mg/dL who have a hist recurrent abdominal pain typical of pancreatitis. Some Typ 1000 mg/dL may, through dietary or alcohol indiscretion, c with massive TG elevations accompanying fasting chylomic niacin therapy on risk of pancreatitis in such situations has Drug therapy is not indicated for patients with Type I hype elevations of chylomicrons and plasma TG, but who have r Inspection of plasma refrigerated for 14 hours is helpful in V hyperlipoproteinemia. [9]

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Table 8. Classification of Hyperlipopr

		L
Type	Lipoproteins Elevated	M
I (rare)	chylomicrons	-
IIa	LDL	-
IIb	LDL, VLDL	-
III (rare)	IDL	TC
IV	VLDL	-
V (rare)	chylomicrons, VLDL	-

TC = total cholesterol; TG = triglycerides; LD
lipoprotein; VLDL = very low-density lipoprot
intermediate-density lipoprotein

up-> = increased or no change

(back to top)

CONTRAINDICATIONS

NIASPAN is contraindicated in patients with a known hypersensit component of this medication, significant or unexplained hepatic ulcer disease, or arterial bleeding.

(back to top)

WARNINGS

NIASPAN preparations should not be substituted for equiv release (crystalline) niacin. For patients switching from in NIASPAN, therapy with NIASPAN should be initiated with qhs) and the NIASPAN dose should then be titrated to the response (see DOSAGE AND ADMINISTRATION).

Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepa in patients who have substituted sustained-release (m di niacin products for immediate-release (crystalline) niacin

NIASPAN should be used with caution in patients who c r of alcohol and/or have a past history of liver disease. Acti unexplained transaminase elevations are contraindicati n

Niacin preparations, like some other lipid-lowering therapies, ha abnormal liver tests. In three placebo-controlled clinical trials in NIASPAN doses ranging from 500 to 3000mg, 245 patients recei duration of 17 weeks. No patient with normal serum transamina

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experienced elevations to more than 3 times the upper limit of n with NIASPAN. In these studies, fewer than 1% (2/245) of NIAS to transaminase elevations greater than 2 times the ULN.

Interim results from a recently completed, long-term extension s patients (617 who were treated for a mean duration of 50 weeks (4/717) of NIASPAN-treated patients with normal serum transan experienced elevations greater than 3 times ULN (one of the fou HMG-CoA reductase inhibitor therapy).

In the placebo-controlled clinical trials and the long-term extens transaminases did not appear to be related to treatment duratio appear to be dose related. Transaminase elevations were revers NIASPAN.

Liver tests should be performed on all patients during therapy w transaminase levels, including AST and ALT (SGOT and SGPT), s treatment begins, every 6 weeks to 12 weeks for the first year, a (e.g., at approximately 6-month intervals). Special attention shc develop elevated serum transaminase levels, and in these patier repeated promptly and then performed more frequently. If the t evidence of progression, particularly if they rise to 3 times the U they are associated with symptoms of nausea, fever, and/or mal discontinued.

Skeletal Muscle

Rare cases of rhabdomyolysis have been associated with concor altering doses (>/=1 g/day) of niacin and HMG-CoA reductase ir rhabdomyolysis have been reported in 124 patients who were tr combination with various HMG-CoA reductase inhibitors. Physicia therapy with HMG-CoA reductase inhibitors and NIASPAN should benefits and risks and should carefully monitor patients for any s pain, tenderness, or weakness, particularly during the initial mo periods of upward dosage titration of either drug. Periodic serur and potassium determinations should be considered in such situ assurance that such monitoring will prevent the occurrence of se

(*back to top*)

PRECAUTIONS

General

Before instituting therapy with NIASPAN, an attempt should be r with appropriate diet, exercise, and weight reduction in obese pa underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, o observed closely during NIASPAN therapy. Frequent monitoring glucose should be performed to ascertain that the drug is produ these organ systems. Diabetic patients may experience a dose-r tolerance, the clinical significance of which is unclear. Diabetic o

should be observed closely. Adjustment of diet and/or hypoglyce necessary.

Caution should also be used when NIASPAN is used in patients w acute phase of MI, particularly when such patients are also recei nitrates, calcium channel blockers, or adrenergic blocking agents

Elevated uric acid levels have occurred with niacin therapy, ther patients predisposed to gout.

NIASPAN has been associated with small but statistically signific platelet count (mean of -11% with 2000mg). In addition, NIASP small but statistically significant increases in prothrombin time (i accordingly, patients undergoing surgery should be carefully eva observed when NIASPAN is administered concomitantly with ant and platelet counts should be monitored closely in such patients

In placebo-controlled trials, NIASPAN has been associated with s significant, dose-related reductions in phosphorus levels (mean Although these reductions were transient, phosphorus levels sho in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through contraindicated in patients with significant or unexplained hepati CONTRAINDICATIONS and WARNINGS) and should be used witl dysfunction.

Information for Patients

Patients should be advised:

- to take NIASPAN at bedtime, after a low-fat snack. Admini is not recommended;
- to carefully follow the prescribed dosing regimen, includinc schedule, in order to minimize side effects (see DOSAGE A
- that flushing is a common side effect of niacin therapy tha weeks of consistent niacin use. Flushing may vary in sever after dosing, and will, by taking NIASPAN® at bedtime, m however, if awakened by flushing at night, to get up slowl feeling faint, or taking blood pressure medications;
- that taking aspirin (approximately 30 minutes before takin anti-inflammatory drug (e.g., ibuprofen) may minimize flu
- to avoid ingestion of alcohol or hot drinks around the time minimize flushing;
- that if NIASPAN therapy is discontinued for an extended le should be contacted prior to re-starting therapy; re-titratic DOSAGE AND ADMINISTRATION ; Table 10);
- to notify their physician if they are taking vitamins or othe containing niacin or related compounds such as nicotinami
- to notify their physician if symptoms of dizziness occur;
- if diabetic, to notify their physician of changes in blood glu

- that NIASPAN tablets should not be broken, crushed or ch whole.

(back to top)

Drug Interactions

HMG-CoA Reductase Inhibitors: See WARNINGS , *Skeletal Mus*

Antihypertensive Therapy: Niacin may potentiate the effects o and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clear clinical relevance of this finding is unclear.

Bile Acid Sequestrants: An *in vitro* study was carried out inves capacity of colestipol and cholestyramine. About 98% of availabl colestipol, with 10 to 30% binding to cholestyramine. These resu or as great an interval as possible, should elapse between the in resins and the administration of NIASPAN.

Other: Concomitant alcohol or hot drinks may increase the sid pruritus and should be avoided around the time of NIASPAN inge nutritional supplements containing large doses of niacin or relate nicotinamide may potentiate the adverse effects of NIASPAN.

Drug/Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determ catecholamines. Niacin may also give false-positive reactions wit (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fer

Niacin administered to mice for a lifetime as a 1% solution in dri carcinogenic. The mice in this study received approximately 6 to mg/day as determined on a mg/m ^{2} basis. Niacin was negative f test. No studies on impairment of fertility have been performed. conducted with NIASPAN regarding carcinogenesis, mutagenesis

Pregnancy

Pregnancy Category C.

Animal reproduction studies have not been conducted with niacin not known whether niacin at doses typically used for lipid disord administered to pregnant women or whether it can affect reprod receiving niacin for primary hypercholesterolemia (Types IIa or I drug should be discontinued. If a woman being treated with niac (Types IV or V) conceives, the benefits and risks of continued th an individual basis.

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Nursing Mothers

Niacin has been reported to be excreted in human milk. Because adverse reactions in nursing infants from lipid-altering doses of n be made whether to discontinue nursing or to discontinue the dr importance of the drug to the mother. No studies have been con nursing mothers.

Pediatric Use

Safety and effectiveness of niacin therapy in pediatric patients (· established. No studies in patients under 21 years of age have b

(*back to top*)

ADVERSE REACTIONS

NIASPAN is generally well tolerated; adverse reactions have bee placebo-controlled clinical trials, flushing episodes (i.e., warmth, tingling) were the most common treatment-emergent adverse e 88% of patients) for NIASPAN. Spontaneous reports suggest tha accompanied by symptoms of dizziness, tachycardia, palpitation sweating, chills, and/or edema, which in rare cases may lead to fewer that 6% (14/245) of NIASPAN patients discontinued due t immediate-release (IR) niacin and NIASPAN, although the propo was similar, fewer flushing episodes were reported by patients w Following 4 weeks of maintenance therapy at daily doses of 150 over the 4-week period averaged 8.56 events per patient for IR NIASPAN.

Other adverse events occurring in 5% or greater of patients trea remotely related to NIASPAN, are shown in Table 9 below.

Table 9 Treatment-Emergent Adverse Events by D Patients; Events Considered At Least Remotely Related t

	Placebo-Controlled St NIASPAN Treatme				
		Recommended Daily Maintenance Doses			
	Placebo (n=157) %	500mg ± (n=87) %	1000mg (n=110) %	1500mg (n=136) %	20((n
Headache	15	5 *	9	11	

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Pain	3	1	2	5	
Pain, Abdominal	3	3	2	3	
Diarrhea	8	6	7	6	
Dyspepsia	8	2	4	5	
Nausea	4	2	5	3	
Vomiting	2	0	2	3	
Rhinitis	7	2	5	4	
Pruritus	1	6	<1	3	
Rash	<1	5	5	4	

Note: Percentages are calculated from the total num column. AEs are reported at the lowest dose where t

† Pooled results from placebo-controlled studies; for mean treatment duration = 17 weeks. Number of NI not additive across doses.

‡ The 500mg, 2500mg and 3000mg/day doses are o daily maintenance dosing range; see DOSAGE AND A

* Significantly different from placebo at $p </= 0.05$; size>5), Fisher's Exact test (cell sizes</=5).
In general, the incidence of adverse events was high to men.

The following adverse events have also been reported with niaci clinical trials or in routine patient management.

Body as a Whole: edema, asthenia, chills

Cardiovascular: atrial fibrillation, and other cardiac arrhythmia orthostasis; syncope; hypotension

Eye: toxic amblyopia, crystoid macular edema

Gastrointestinal: activation of peptic ulcers and peptic ulceratio

Metabolic: decreased glucose tolerance; gout

Musculoskeletal: myalgia

Nervous: dizziness, insomnia

Skin: hyper-pigmentation; maculopapular rash; acanthosis nig sweating

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Other: migraine

Clinical Lab rat ry Abnormalities

Chemistry: Elevations in serum transaminases (see WARNINGS fasting glucose, uric acid, total bilirubin, and amylase; reduction

Hematology: Slight reductions in platelet counts and prolongati WARNINGS)

(back to top)

DRUG ABUSE AND DEPENDENCE

Niacin is a non-narcotic drug. It has no known addiction potentia

(back to top)

OVERDOSE

Supportive measures should be undertaken in the event of an ov

(back to top)

DOSAGE AND ADMINISTRATION

NIASPAN should be taken at bedtime, after a low-fat snack, and according to patient response. Therapy with NIASPAN must be ir to reduce the incidence and severity of side effects which may o recommended dose escalation is shown in Table 10 below.

Table 10. Recommended Dosi

	Week(s)	Daily dose	NIAS
INITIAL TITRATION SCHEDULE	1 to 4	500mg	1 NIA a
	5 to 8	1000mg	2 NIA a
	*	1500mg	2 NIA t 3 NIA

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			a
	*	2000mg	2 NIA t 4 NIA a

* After Week 8, titrate to patient response i
If response to 1000mg daily is inadequate,
to 1500mg daily; may subsequently increas
2000mg daily. Daily dose should not be inci
than 500mg in a 4-week period, and doses
daily are not recommended. Women may re
doses than men.

Maintenance Dose:

The daily dosage of NIASPAN should not be increased by i week period. The recommended maintenance dose is 100(2000mg (two 1000mg tablets or four 500mg tablets) onc greater than 2000mg daily are not recommended. Women may i doses than men (see CLINICAL PHARMACOLOGY , *Gender Effect*

If lipid response to NIASPAN alone is insufficient, or if higher dos tolerated, some patients may benefit from combination therapy an HMG-CoA reductase inhibitor. (see WARNINGS , PRECAUTION Concomitant Therapy below, and CLINICAL PHARMACOLOGY , NI

Flushing of the skin (see ADVERSE REACTIONS) may be reduce pretreatment with aspirin (taken 30 minutes prior to NIASPAN d inflammatory drugs. Tolerance to this flushing develops rapidly c weeks. Flushing, pruritus, and gastrointestinal distress are also g increasing the dose of niacin and avoiding administration on an e

Equivalent doses of NIASPAN should **not** be substituted for susta release, timed-release) niacin preparations or immediate-release WARNINGS). Patients previously receiving other niacin products recommended NIASPAN titration schedule (see Table 10), and th individualized based on patient response. Single-dose bioavailab that NIASPAN tablet strengths are not interchangeable.

If NIASPAN therapy is discontinued for an extended period, reins include a titration phase (see Table 10).

NIASPAN tablets should be taken whole and should not be broke swallowing.

Conc mitant Therapy

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Preliminary evidence suggests that the lipid-lowering effects of N enhanced with an HMG-CoA reductase inhibitor, e.g., lovastatin, fluvastatin. Additive effects on LDL-C are also seen when niacin binding resins. (see WARNINGS and PRECAUTIONS , Drug Intera

Dosage in Patients with Renal or Hepatic Insuffi

Use of NIASPAN in patients with renal or hepatic insufficiency ha contraindicated in patients with significant or unexplained hepati be used with caution in patients with renal insufficiency (see WA

(*back to top*)

HOW SUPPLIED

NIASPAN is supplied as unscored, off-white capsule-shaped table 1000mg of niacin in an extended-release formulation. Tablets ar and the tablet strength (500, 750 or 1000) on the other side. Ta 100 as shown below.

500mg tablets: bottles of 100 - NDC# 60598-001-01

750mg tablets: bottles of 100 - NDC# 60598-002-01

1000mg tablets: bottles of 100 - NDC# 60598-003-01

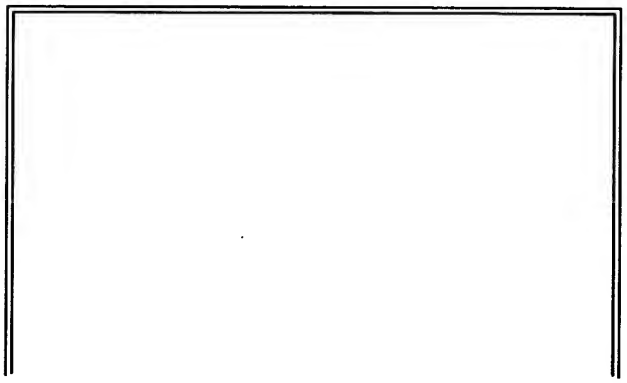
Store at room temperature, (20 to 25°C or 68 to 77°F).

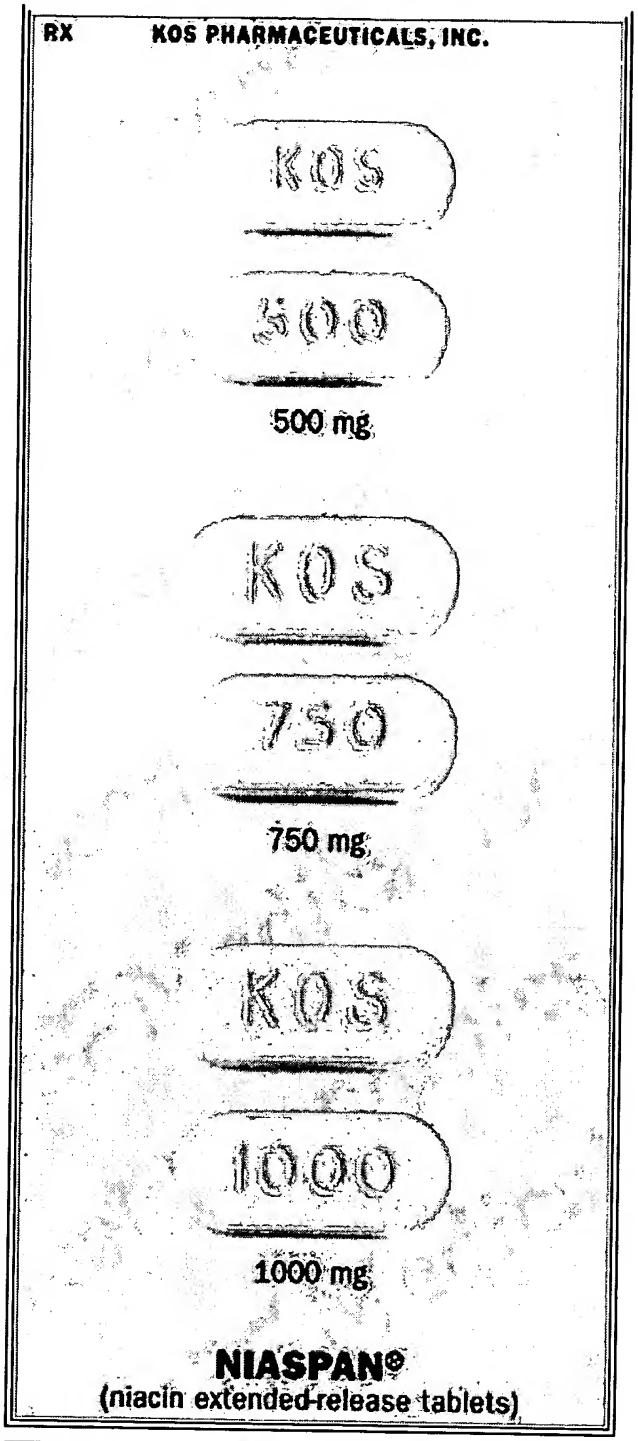
(*back to top*)

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape not depict actual *or relative* size.

The product samples shown here have been supplied by the mar full color by PDR as a quick-reference identification aid. While ev assure accurate reproduction, please remember that any visual i considered preliminary. In cases of poisoning or suspected overc should be verified by chemical analysis.





(back to top)

REFERENCES

1. Bostom AG et al. *JAMA* . 1996; 276:544-548.
2. The Coronary Drug Project Research Group. *JAMA* . 1975;
3. Canner PL et al. *J Am Coll Cardiol* . 1986; 8(6):1245-1255
4. Blankenhorn DH et al. *JAMA* . 1987; 257(23):3233-3240.
5. Cashin-Hemphill L et al. *JAMA* . 1990; 264(23):3013-3017

f e f e b h e e e e ec

6. Brown G et al. *NEJM* . 1990; 323:1289-1298.
7. Pasternak RC et al. *Annals Int Med* . 1996; 125:529-540.
8. Summary of the Second Report of the National Cholesterol Expert Panel on Detection, Evaluation, and Treatment of H (Adult Treatment Panel II), *JAMA* . 1993;269:3015-3023.
9. Nikkila EA, In: *The Metabolic Basis of Inherited Disease* . 5 642.

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